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Imipenem-Resistant *Nocardia cyriacigeorgica* Infection in a Child with Chronic Granulomatous Disease▽

Andrés Hagerman,[1] Verónica Rodríguez-Nava,[2] Patrick Boiron,[2] Pierre-Alex Crisinel,[1] and Klara M. Posfay-Barbe[1]*

Department of Pediatrics, Children's Hospital of Geneva, University Hospitals of Geneva, Geneva, Switzerland,[1] and Université de Lyon and UMR CNRS 5557, Center for Microbial Ecology, Opportunistic Pathogens Bacterial and Environment Research Group, French Observatory for Nocardiosis, Faculté de Pharmacie, Université Lyon 1, Ecole Nationale Vétérinaire de Lyon, Marcy l'Etoile, France[2]

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***Nocardia* spp. can lead to local or disseminated infections, especially in immunocompromised patients. Combination therapy of amikacin and imipenem is commonly used to treat severe nocardial infections. We describe a patient with imipenem-resistant *Nocardia cyriacigeorgica*, which, to our knowledge, has not been previously reported among isolates of this species.**

CASE REPORT

A 9-year-old boy with an X-linked chronic granulomatous disease (CGD) was admitted in our hospital after a 5-day history of fever (>39°C), cough, rhinorrhea, vomiting, and loose stools, as well as macroscopic hematuria. His primary care physician had prescribed empirically amoxicillin-clavulanate 3 days prior to admission after finding mildly elevated leukocytosis (17.3 ×G/liter) and a serum C-reactive protein (CRP) level of 158 mg/liter. The patient had a negative rapid streptococcal test of the throat and a urinalysis showing hematuria and proteinuria. A urine culture was negative. A possible glomerulonephritis without edema or hypertension was suspected, and he was admitted.

He had received an allogeneic bone marrow transplantation from his sister at the age of 1 year, with a neutrophil activity of 7% (NADPH oxidase) 2 years prior. Despite this, he never had a serious infection. He was prescribed routine trimethoprim-sulfamethoxazole and itraconazole prophylaxis at least 6 months prior to this episode, but his parents admitted bad compliance.

On admission, the physical examination revealed that the child was not septic but was febrile at 38.8°C, with a normal physical exam. His white blood cell count was 12.4 ×G/liter, with 75.5% segmented and 9% nonsegmented neutrophils, hemoglobin at 12.6 mg/dl, platelets at 301,000/mm^3, CRP at 97 mg/liter, procalcitonin at 0.58 μg/liter, and an erythrocyte sedimentation rate of 103 mm/h. Proteinuria was confirmed, with microscopic hematuria and normal glomerular filtration rate. Abdominal ultrasonography was compatible with acute glomerulonephritis. The pediatric nephrologists concluded that this child had a glomerulonephritis of unknown etiology, with a subsequent spontaneous resolution of the proteinuria. Because of the persistent fever in an immunocompromised patient, a chest radiography and computer tomography (CT) scan were requested and showed an opacity in the upper left lobe of the lung. A bronchoalveolar lavage (BAL) was performed, and while the microbiological results were being awaited, an empirical treatment with intravenous amoxicillin-clavulanate was started on hospital day 1. Because of persisting fever, intravenous antibiotics were changed on day 2 to intravenous imipenem (100 mg/kg of body weight/day) and trimethoprim-sulfamethoxazole (15 mg/kg/day of trimethoprim) to cover broadly opportunistic microorganisms. Voriconazole was added on day 3. He rapidly improved clinically after that day.

Routine cultures, including those for fungal, viral, and mycobacterial organisms, in the BAL fluid were initially negative. PCR in the BAL fluid for multiple respiratory virus (including adenovirus, enterovirus, influenza A virus, pandemic influenza A virus [H1N1/09], influenza B virus, metapneumovirus, parainfluenza virus, rhinovirus, and respiratory syncytial virus [RSV]), *Mycobacterium tuberculosis*, *Chlamydia pneumoniae*, and *Mycoplasma pneumoniae* and a broad-range bacterial PCR in the blood were also negative. A tuberculin skin test, gamma interferon release assay, antistreptolysin O titer, and mannan and galactomannan tests were also negative. Culture from the BAL fluid from hospital day 1 grew 9 days later. Small chalky white colonies were observed on blood agar plates. These colonies showed vegetative white aerial hyphae with branch points. Preliminary morphological characteristics were compatible with *Nocardia* species. No other organism grew on hospital day 1 BAL cultures. Consequently, treatment was changed on day 9 to intravenous imipenem at 100 mg/kg/day and amikacin at 20 mg/kg/day for a suspected disseminated nocardiosis (pulmonary, renal, and intestinal) despite the good general status of the patient, and itraconazole prophylaxis was restarted. Blood cultures and urine culture for *Nocardia* spp. were negative. A positron emission tomography (PET) scan showed pathological and nonspecific hypermetabolism in the upper left lobe but also an inflammatory process in the supraclavicular lymph node. Cerebral magnetic resonance imaging (MRI) did not show intracerebral lesions. Echocar-

* Corresponding author. Mailing address: Children's Hospital of Geneva, University Hospital of Geneva, 6 Rue Willy-Donzé, 1211 Geneva, Switzerland. Phone: 41 22 382 4562. Fax: 41 22 382 5490. E-mail: Klara.PosfayBarbe@hcuge.ch.

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TABLE 1. Described patient's *Nocardia cyriacigeorgica* susceptibility table

Antibiotic	MIC(s) (μg/ml)[a]
Amikacin	≤4 (S)
Trimethoprim-sulfamethoxazole	1/19 (S)
Linezolid	2 (S)
Cefotaxime	8 (S)
Amoxicillin-clavulanate	>16 (R)
Imipenem	16 (R)
Meropenem	16*
Ertapenem	16*
Doripenem	32*
Ciprofloxacin	≥4 (R)
Tigecycline	≤1*

[a] S, susceptible; R, resistant; *, no interpretation of susceptibility available with the method used.

diography was normal. The *Nocardia* sp. strain was partially amplified, sequenced, and identified by using a 600-nucleotide (nt) fragment of the 16S rRNA gene as previously described by Rodriguez-Nava et al. (9). The susceptibility pattern was tested by using the broth microdilution method following the M24A guidelines from the Clinical and Laboratory Standards Institute (CLSI). The results were recorded after 72 h and interpreted according to the MIC breakpoints published by CLSI (8). The sequenced fragment presented 100% similarity to the *Nocardia cyriacigeorgica* type strain DSM 44484.

Antibiotics susceptibilities are shown in Table 1. Because of the resistance pattern, imipenem was then discontinued and trimethoprim-sulfamethoxazole at 20 mg/kg/day (of trimethoprim), combined with amikacin at 20 mg/kg/day, was restarted on day 21. A repeat chest radiograph showed significant resolution of the opacity. The patient was discharged 50 days after admission. The patient has completed 3 months of therapy with amikacin and is currently receiving trimethoprim-sulfamethoxazole for at least 12 months.

Nocardia spp. can cause severe infections in patients with CGD, usually in the lungs (4). Pulmonary nocardiosis can be either acute or chronic or both (2). Radiographic findings include infiltrates, nodules, cavities, and empyema (2, 4). However, images are nonspecific and may mimic other infections, such as those caused by *Aspergillus* spp., *Staphylococcus* spp., or *Mycobacterium*, explaining why broad-spectrum antimicrobial coverage is usually initiated, as with our patient. Extrapulmonary disease can complicate up to 50% of cases of pulmonary nocardiosis: cerebral abscess, for example, should be actively examined by MRI (2, 4). Patients receiving sulfonamide prophylaxis are less likely to have disseminated nocardiosis (4); however, some patients may have nocardiosis despite trimethoprim-sulfamethoxazole prophylaxis (2, 7). Sulfonamide-based regimens generally maintain their efficacy for treatment in patients who previously received sulfonamide prophylaxis. Combination therapy with carbapenem (either imipenem or meropenem) or an expanded-spectrum cephalosporin with amikacin is recommended for severely ill patients (1). Our patient was clinically stable, and the efficacy of treatment could not be established by clinical response. Knowing that nocardiosis has a tendency to recur and that it has high morbidity and mortality rates in immunosuppressed patients, we treated our patient with a combination therapy. Combining imipenem and amikacin appears to be more effective than trimethoprim-sulfamethoxazole alone because of a synergistic effect (1, 2). Furthermore, amikacin and imipenem have a bactericidal effect, which contrasts with the bacteriostatic effect of sulfonamides. Resistance and therapeutic failures may require using other antimicrobials, such as linezolid, tigecycline, and moxifloxacin: these antimicrobials have shown promising results in adults (6).

Although identification may be useful to predict susceptibility patterns of the *Nocardia* species, this case shows that it is paramount to perform timely susceptibility testing, as identification may not always predict antimicrobial efficacy. *N. cyriacigeorgica* was first described by Yassin and colleagues in 2001 (10). It is a newly named but long-recognized agent of human disease, and only few cases have been published using this new name (3). *N. cyriacigeorgica* belongs to the group of *Nocardia* spp. previously classified as having a type VI drug pattern (3). It appears that *N. cyriacigeorgica* has a drug pattern identical to the *N. asteroides* drug susceptibility pattern type VI, which accounts for approximately 60% of clinical *N. asteroides* complex strains (5). In addition to having sulfonamide susceptibility, type VI complex strains are generally susceptible to amikacin, broad-spectrum cephalosporins, imipenem, and linezolid but resistant to amoxicillin-clavulanate, ampicillin, ciprofloxacin, and clarithromycin (3). Linezolid appears to be the most effective agent *in vitro* against *Nocardia*, but clinical experience is limited (5). Other complexes, such as those corresponding to the highly antimicrobial-resistant *N. transvalensis* (type IV) and *N. farcinica* (type V), have been described.

While the usual combination therapy of amikacin and imipenem is commonly used to treat severe nocardial infections, this case report suggests that a three-drug regimen (trimethoprim-sulfamethoxazole, amikacin, and ceftriaxone or imipenem), as suggested by some authors (1, 2), should be started initially in patients with serious disease and/or disseminated infection until species and susceptibility patterns are determined. Moreover, there are no previous published reports of imipenem resistance in *N. cyriacigeorgica* strains, and susceptibilities may not be routinely determined, due to the assumption that all strains will be susceptible to imipenem. Thus, we recommend antimicrobial susceptibility testing for all *Nocardia* spp.

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